(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 November 2007 (08.11.2007)

PCT

(10) International Publication Number
WO 2007/126865 A2

(51) International Patent Classification:
A61K 31/519 (2006.01)

(21) International Application Number:
PCT/US2007/007650

(22) International Filing Date: 27 March 2007 (27.03.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/787,390 30 March 2006 (30.03.2006) US

(71) Applicant *(for all designated States except US)*: **PATRIN PHARMA** [US/US]; 7817 Babb Avenue, Skokie, IL 60077 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **TRIVEDI, Jay, S.** [US/US]; 7817 Babb Avenue, Skokie, IL 60077 (US). **QUINN, Robert, P.** [US/US]; 801 Cox Mill Road, Concord, NC 28027 (US).

(74) Agents: **DAVIDSON, Clifford, M.** et al.; Davidson, Davidson & Kappel, LLC, 485 Seventh Avenue, 14th Floor, New York, NY 10018 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: LEUKOTRIENE ANTAGONISTS VIA NASAL DRUG DELIVERY

(57) Abstract: The invention provides pharmaceutical compositions for leukotriene antagonists for nasal and ocular delivery routes. These compounds are useful as anti-asthmatic, anti-allergic, anti-inflammatory and cytoprotective agents. They are also useful in treating hepatitis, endotoxemia and psoriasis.

WO 2007/126865 A2

LEUKOTRIENE ANTAGONISTS VIA NASAL DRUG DELIVERY

DESCRIPTION

[0001] The present invention relates to the use of pharmaceutical agents, and pharmaceutical compositions particularly comprising of leukotriene agents and pharmaceutically acceptable salts thereof, more particularly unsaturated hydroxyalkylquinoline acids and their salts in the treatment of medical conditions using nasal delivery route for the administration.

BACKGROUND OF THE INVENTION

[0002] The compound that exhibits the inhibition of cycteinyl leukotriene cycsLT1 receptor is leukotriene antagonist. Such compounds are described in U.S. patent 5,565,473, hereby incorporated by reference. An example of such compound is Montelukast sodium, chemically known as *R* -(*E*)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl] propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt. The particular compound is used in a form of oral tablet, chewable tablet and oral granules to treat prophylaxis and chronic treatment of asthma in adults and children. See the Physician's Desk Reference 58th Edition, 2004, the disclosure of which is hereby incorporated by reference. It is also indicated in the treatment of relief of symptoms of seasonal allergic rhinitis in adults and children.

[0003] The nasal delivery route for drug delivery is of particular interest because of the need to develop a non oral, nonparenteral route. In addition, drugs that are particularly subject to destruction by the gastrointestinal fluids can utilize nasal delivery route. Nasal mucosa has been shown to be amenable to the systemic absorption of certain drugs, particularly poorly absorbed drugs via oral delivery.

[0004] The adult nasal cavity has about 20 ml capacity, with a large surface area (about 180 cm^2) for drug absorption afforded by the microvilli present along the

pseudostratified columnar epithelial cells of the nasal mucosa . See Sarkar, M.A.: Drug Metabolism in the Nasal Mucosa. Pharm. Res. 9:1-9, 1992 and Donovan, M.D., Flynn, G.L., and Amidon, G.L.: The molecular Weights of Nasal Absorption: The Effect of Absorption Enhancers. Pharm. Res., 8: 808-815, 1990, the disclosures of which are hereby incorporated by reference. The nasal tissue is highly vascularized, providing an attractive site for rapid and efficient systemic absorption. Another great advantage of nasal route is that it avoids first pass metabolism by the liver. For some drugs, intranasal bioavailability has been shown to be comparable to that of injection. In addition, various formulation adjuncts, such as surface active agents and bioavailability enhancers are used to enhance nasal absorption.

[0005] It has been found that Montelukast, sodium and other physiologically acceptable salts would exhibit particularly advantageous and surprising effect when the corresponding formulations are applied directly in the nose and or to the conjunctival sac of the eye.

[0006] The elimination or the marked relief has thus been achieved not only in allergy related rhinitis, but also in asthma relief.

[0007] It is surprising in this context that local nasal application also has a favorable effect on the mucous membrane of the eye (elimination or the relief of reddening of the eye and of eye irritation) so that the additional use of eye drops is frequently superfluous.

[0008] Other indications for the application/use of the invention are, for example: non-specific conjunctivitis, allergy related conjunctivitis, allergic pblepharoedema, catarrhal conditions in the eye or the nose, coryza.

[0009] Furthermore, the invention provides a way to overcome typical problems such as swallowing which can arise with the oral dosing of tablet, capsule, chewable tablet and granule for suspension. It was surprisingly found that in trial subjects this

was no longer an issue when the Montelukast sodium formulations of the invention were sprayed into the nose. As a result, it is possible in this manner to apply solutions or dry powder of Montelukast, sodium salt and other physiologically acceptable salts nasally without swallowing impairment. In addition, subjects reported a faster onset of relief from the symptoms as compared to the oral dosing.

[0010] Therefore, the object of the present invention is to provide a well tolerated and improved remedy based on the Montelukast, sodium or other salts for the treatment both of the allergy related and asthma related symptoms via nasal delivery route.

[0011] A further object of the present invention is to provide medical formulations which are adapted to direct application to nasal and eye tissue.

[0012] The preferred embodiment of the invention is a sterile and stable aqueous solution of the drug or one or more of its salts which can be used in the form of drops, ointments, creams, gels, dry insufflatable powders or, in a particularly preferred embodiment, in the form of a spray (preferably in a nasal spray). The spray can be formed by the use of a conventional spray-squeeze bottle or a pump vaporizer. In addition, it is possible to use compressed gas aerosols. For an example, 0.01 to 10 mg, more preferably 0.1 to 5 mg of Montelukast, sodium or other salt should be released per individual actuation.

[0013] Solvents which may preferably be used for the formulations of the invention are: water, water containing physiologically relevant salt (e.g. Sodium or potassium chloride), saturated aliphatic mono and polyvalent alcohols which contain 2-4 carbon atoms (for example ethanol, propanol, 1,2-propylene glycol (glycerine), liquid polyglycols (molecular weight 100-600), physiologically acceptable oils.

[0014] The solutions or formulations preferably contain effective amounts of pharmaceutically acceptable preservatives and stabilizers. These include, for

example: ethylene diamine tetra-acetic acid and their alkali salts (for example dialkali salts such as disodium, calcium, sodium-calcium salt), lower alkyl p-hydroxybenzoates, chlorohexidine (for example acetate or gluconate), phenyl mercury borate, sodium or potassium benzoate. Furthermore, it may contain, for example "thimerosal" (sodium-(2-ethylmercurithio)-benzoate) in 0.001 to 0.05, preferably in an amount of 0.001 to 0.03 % (weight/volume in liquid formulations, otherwise weight/weight). Other suitable preservatives are: pharmaceutically acceptable quaternary ammonium compounds, such as generally known cetrimide, benzethonium chloride and myristyl-picolinium chloride. These compounds can be used either as single entity or in a combination in an amount of 0.001 to 0.05 % total (weight/volume in liquid formulations, otherwise weight/weight), preferably in an amount of 0.001 to 0.03%.

[0015] The formulations of the invention (solutions, suspensions, oily solutions or suspensions, ointments, emulsions, microemulsions, micellar solutions, creams, gels, aerosol dosage) contain 0.0001 to 10, preferably 0.001 to 7, in particular 0.001 to 5% (weight to weight) of Montelukast (base). If the pharmaceutically acceptable salt of Montelukast is present, the amounts should be recalculated as necessary to give the amounts of Montelukast itself mentioned above. In the case of the eye drops, the same Montelukast concentrations apply as in the case of nasal forms.

[0016] In the case of powders, the concentration of Montelukast is 0.0001 to 3% by weight related to the solid carrier substances. For pharmaceutically acceptable salts of Montelukast, the amounts should be recalculated as necessary to give the amounts of Montelukast itself mentioned above.

[0017] In the case of solutions, the dosage per nostril is, for example 0.01 to 0.5 ml, in particular 0.05 to 0.2 ml. Such a dosage should be applied once to several times, preferably 1-3 times per day.

[0018] In the case of use at the eye (eye drops), the dosage is for example 1 drop (approximately 0.5ml) of the solution or the corresponding amounts of the semi-solid formulation form. Such dosage form should be applied once to several times, preferably 1-3 times per day.

[0019] The amounts of preservatives in the formulations (solutions, suspensions, ointments etc.) are between 0.001 to 0.5, preferably 0.01 gram per 100 ml of solution/suspension or 100 g of formulation.

[0020] In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/weight of the formulation.

[0021] Further auxiliary substances which may, for example, be used for the formulations of the invention are: polyvinyl pyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan fatty acid esters (for example polyethoxylated sorbitan trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides, polyethoxylated fatty alcohols. In this context, polyethoxylated means that the relevant substances contain polyoxyethylene chains, the degree of polymerization of which is generally between 2 to 40, in particular between 10 to 20. These substances are preferably used to improve the solubility of the Montelukast components.

[0022] In the case of dosage forms containing water, it is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, NaCl.

[0023] The isotonization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretion. Other isotonization agents used but not limited to are Glucose, saccharose, sucrose, glycerine, 1,2-propylene glycol, sorbitol.

[0024] Moreover, it is possible to add thickening agents to the solutions to prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.2 to 5, preferably 2 mPa.s. Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

[0025] In the event of the use of hydroxypropyl cellulose, 0.1% by weight are, for example, used for this purpose.

[0026] It is also possible to add to the formulations buffer substances such as citric acid / sodium hydrogensulphate borate buffer, phosphates (sodium hydrogenorthophosphate, disodium hydrogenphosphate), tromethamol or equivalent conventional buffers in order, for example, to adjust the formulation to a pH value of 5.5 to 7.5, preferably 6.0 to 7.1.

[0027] In the case of solutions and suspensions, the maximum total concentration of active agent and buffer should be less than 5%, in particular less than 2% (weight/volume).

[0028] For the nasal application a solution or suspension is preferably used which is applied as an aerosol, i.e. in the form of a fine dispersion in air or in another conventional carrier gas, for example by means of a conventional pump vaporizer.

[0029] Application as a dosage aerosol is, however, also possible. Dosage aerosols are defined as being pressure packings which contain the Montelukast or its

salts in the form of a solution or suspension in a so-called propellant. Propellants are pressurized liquid chlorinated, fluorinated hydrocarbons or mixtures of various chlorinated, fluorinated hydrocarbons as well as propane, butane, isobutane or mixtures of these among themselves or with chlorinated, fluorinated hydrocarbons which are gaseous at atmospheric pressure and room temperature. The pressure packing has a dosage valve which, on actuation, releases a defined amount of the solution or suspension of the medicament. The subsequent very sudden vaporization of the propellant tears the solution or suspension of Montelukast and all of its pharmaceutically relevant salts into the finest droplets or minute particles which can be sprayed into the nose or which are available for inspiration into the nose. Certain plastic applicators are used to actuate the valve and to convey the sprayed suspension into the nose. Propellants that may, however, also be used are: CO_2, nitrous oxide and compressed air.

[0030] In the case of application as an aerosol, it is also possible to use a conventional adapter.

[0031] When suspensions are used, the maximum particle size of the solid substances (Montelukast + auxiliary substances) should not exceed 30 micrometer.

[0032] In the case of use in the form of an insufflatable powder, the maximum particle size of the substances should not be greater than 20 micrometer.

[0033] In the case of insufflatable powders, what occurs is, for example, a vaporizing of solid Montelukast or its salts. In this case the Montelukast or its salt is, for example, mixed with inert carrier substances or drawn up onto inert carrier substances. Carrier substances which may, for example, be used are: sugars such as glucose, saccharose, lactose and fructose. Also starches or starch derivatives, oligosaccharides such as dextrins, cyclodextrins and their derivatives, polyvinylpyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives (for example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium

carbonate, calcium phosphate. The concentration of Montelukast or pharmaceutically acceptable salts is 1 part by weight to 50 to 500,000 parts by weight of carrier substance (0.0005 to 5% of Montelukast or salt).

[0034] The following examples describe and illustrate the processes and products of the present invention. These examples are intended to be merely illustrative of the present invention, and not limiting thereof in either scope or spirit. Those skilled in the art will readily understand that variations of the materials, conditions, and processes described in these examples can be used.

EXAMPLE 1 - Nasal spray or nasal drops or eye drops with 1.1% Montelukast sodium as active ingredient

[0035] The following are dissolved, in the following order, into 90 g of water: 1 g of Montelukast sodium, 0.05 g of edeticacid disodium salt. 2 H_2O, 0.68 g of sodium chloride, 0.01 g of alkyl-benzyldimethylammonium chloride (benzalkonium chloride), 0.05 g of citric acid, 0.65 g of sodium monohydrogen-phosphate. 12 H_2O as well as 0.1 g of hydroxypropylmethyl cellulose.).

[0036] The solution obtained above is carefully mixed. The pH of the filtrate is adjusted to pH 6.8 ± 0.4, if necessary. The solution is filtered through a membrane filter of pore size 0.2 micrometer. The first 5 ml of filtrate is discarded. The remaining filtrate is filled into plastic bottles which are closed with a conventional spray insert or into plastic or glass bottles with a conventional pump sprayer. In the latter case, pumps with nasal spray inserts are, for example used, which spray about 0.15 ml of solution per actuation. In this manner, 1.65 mg of Montelukast sodium is sprayed into the nose per actuation in the form of the solution.

[0037] If the above obtained filtrate is filled into the bottles with dropper pipettes conventionally used for nasal drops or eye drops, the solution can be dripped into the nose or eye using a dropper pipette.

EXAMPLE 2 - Nasal Ointment with 1% of Montelukast sodium

[0038] 50 g of polyoxyethylene stearate, 28 g of cetylstearyl alcohol, 200g of white petroleum jelly (Vaseline), 150g of liquid paraffin and 5 g of silicon oil are melted together to approximately 80°C in a beaker heated with a water bath. To this melt, 1.25 g of p-hydroxybenzoic acid methyl ester and 0.5 g of p-hydroxybenzoic acid propyl ester were added under constant stirring. In a separate beaker heated to 70°C with a water bath, 10g of Montelukast sodium in 510 g of water with 1.40 g of p-hydroxybenzoic acid methyl ester and 0.6 g of p-hydroxybenzoic acid propyl ester were mixed under constant stirring. The content of the second beaker was added to the first beaker under high speed stirring and with a frequent mixing with a homogenizer to obtain an emulsion. The mixture was allowed to cool to room temperature under high speed stirring and under frequent homogenization to create an ointment.

[0039] The ointment can be filled into tubes which have a tubular extension beyond the thread and are thus particularly suitable for applying the ointment into the nose.

EXAMPLE 3 - Dosage aerosol giving off 1 mg of Montelukast sodium per stroke

[0040] About 8.0 kg of a mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2dichlorotetrafluoroethane are cooled to about -55°C in an appropriate cooling vessel. A mixture of 0.086 kg of precooled sorbitantrioleate and 0.8600 kg of precooled trichlorofluoromethane are dissolved with stirring into this mixture at -55°C, 0.1375 kg of micronized Montelukast sodium and 0.1375 kg of micronized lactose are then incorporated in portions into the solution thereby obtained with intensive stirring. The total weight of the suspension thereby obtained is made up to 9.547 kg through addition of more of the mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane cooled to about -55°C.

[0041] Following closure of the cooling vessel the suspension is again cooled to about -55°C under intensive stirring. It is then ready to be filled.

[0042] With continued stirring the suspension is filled into the conventional suitable aluminum monobloc tins. The monobloc tins are closed immediately after the suspension has been filled using conventional dosage valves which release 0.05 ml of suspension per valve actuation. Actuation of the valve thus releases 1 mg of Montelukast sodium. Presentation is effected in conjunction with a conventional applicator which permits introduction of the active substance into the nose of the patient.

EXAMPLE 4 - Eye drops with 0.1% of Montelukast sodium

[0043] 140 g of polyvinylalcohol (trade name for example: Mowiol 26-88 / Hoechst AG, Frankfurt 80) are stirred into 4 liters of cold water for injection, the suspension is heated to 90°C and left at this temperature for 30 minutes. After cooling, the solution obtained is mixed with the following solutions:

[0044] 10 g of Montelukast sodium in 1 liter of water for injection, 0.2 g of phenyl mercuric nitrate in 2 liters of water for injection, 70 g of sodium chloride in 1 liter of water for injection.

[0045] The mixture is adjusted to a pH value of 6.8 through addition of 0.1 N sodium hydroxide or 0.1N hydrochloric acid solution.

[0046] Following careful mixing the solution is filtered through a membrane filter of pore size 0.2 micrometer with glass fiber pre-filter and filled into sterile eye drop bottles under aseptic conditions after discarding a first 500 ml of filtrate.

EXAMPLE 5 - Clinical experience with topical Montelukast

[0047] It is hypothesized that two apparently separate mechanisms that mucous membrane cells use to keep their surfaces clear can be observed clinically. The first mechanism, mucociliary clearance, appears to operate via the coordinated action of respiratory mucous membrane cells. This is the clinically well understood mechanism by which cells of the sinus and nasal linings (as well as the lining of the tracheobronchial system) produce a protective blanket of mucus which is then "swept out" to clear the airways. This sweeping motion is the standard explanation for the ability of the sinuses, lungs, middle ear and other areas to keep themselves clear, and is an established part of the art of medicine. Based on years of clinical observation, applicants have developed the hypothesis that there is a second mucous membrane mechanism that actively provides aeration and releases surface tension between opposing mucous membrane cells. Clinically, it appears to be confined to anatomic areas in which boggy mucous membranes sometimes stick together: in the "valve" areas located in the upper part of the nostril, between the nasal turbinates and the floor of the nose, in the clefts on the lateral wall of the nasal cavities where the sinus openings are located, in the upper recesses of the nasal cavity in the areas innervated by the olfactory nerves, in the posterior nasal cavity as it opens into the nasopharynx, and in the nasopharynx itself near the Eustachian tube orifices. This clinical aeration/release of surface tension occurs after topical treatment with montelukast but does not occur immediately. This delay suggests that it is not merely a surfactant effect on mucous membrane cells. The time period over which it occurs suggests that it might occur because of direct aeration of mucous membrane surfaces by gas generation from within the cells. (This may be directly or indirectly the result of breakdown products of free radicals such as molecular nitric oxide, producing nitrogen and oxygen). This hypothesis is offered for the sole purpose of providing a possible explanation concerning the efficacy of methods and formulations in accordance with the invention, and is not meant to limit the invention or the appended claims in any way.

What is claimed is:

1. A pharmaceutical composition for treating a disease selected from the group consisting of asthma, allergy, rhinitis, and inflammatory disease conditions in humans consisting essentially of a therapeutically effective amount of leukotriene antagonist, more particularly unsaturated hydroxyalkylquinoline acids, and pharmaceutical salts thereof formulated for intranasal administration.

2. The pharmaceutical composition of claim 1, wherein at least one of the said hydroxyalkylquinoline acids and pharmaceutical salts is Montelukast Sodium.

3. The pharmaceutical composition of claim 1, wherein a unit dose of the composition is therapeutically effective following intranasal administration to a human to reduce symptoms of asthma in the human.

4. The pharmaceutical composition of claim 1, which is therapeutically effective following intranasal administration to a human to reduce symptoms of allergy in the human.

5. The pharmaceutical composition of claim 1, which is therapeutically effective following intranasal administration to a human to reduce symptoms of inflammation in the human.

6. The pharmaceutical composition of claim 1, which is therapeutically effective following intranasal administration to a human suffering from psoriasis to reduce symptoms of psoriasis.

7. The pharmaceutical composition of claim 1, which is therapeutically effective following intranasal administration to a human to reduce symptoms of endotoxemia in the human.

8. The pharmaceutical composition of claim 3, which is therapeutically effective in the human within 3 hours following intranasal administration.

9. The pharmaceutical composition of claim 4, which is therapeutically effective in the human within 3 hours following intranasal administration.

10. The pharmaceutical composition of claim 1, wherein said composition is an aqueous solution.

11. The pharmaceutical composition of claim 10, wherein said aqueous solution is selected from the group consisting of aqueous gels, aqueous suspensions, aqueous liposomal dispersions, aqueous emulsions, aqueous microemulsions and combinations thereof.

12. The pharmaceutical composition of claim 1, wherein said composition is non-aqueous solution.

13. The pharmaceutical composition of claim 12, wherein said non-aqueous solution is selected from the group consisting of non-aqueous gels, non-aqueous suspensions, non-aqueous liposomal dispersions, non-aqueous emulsions, non-aqueous microemulsions and combinations thereof.

14. The pharmaceutical composition of claim 1, wherein said composition is a powder formulation.

15. The pharmaceutical composition of claim 14, wherein said composition is selected from the group consisting of simple powder mixtures, powder microspheres, coated powder microspheres, and combinations thereof.

16. The formulation of claim 2, comprising 0.01 to 10 mg, more preferably 0.1 to 5 mg of Montelukast per unit dose.

17. The formulation of claim 1, further comprising an effective amount of a buffer to maintain the formulation to a pH value of 5.5 to 7.5, preferably 6.0 to 7.1, and an effective amount of a preservative.

18. The formulation of claims 1, 16 and 17 which is in the form of a solution, further comprising an effective amount of a pharmaceutically acceptable thickening agent to provide the solution a viscosity of about 1.2 to 5, preferably 2 mPa.s.

19. The formulation of claim 17, wherein the maximum total concentration of active agent and buffer should be less than 5%, in particular less than 2% (weight/volume).

20. The formulation of claims 1 – 10 and 16, which is in the form of a solution or suspension applied as an aerosol in the form of a fine dispersion in air or in another conventional carrier gas, for example by means of a conventional pump vaporizer.

21. A method of treating asthma, allergy, rhinitis or inflammatory disease condition in humans comprising administering the pharmaceutical composition of claims 1 - 20 to a human patient in need thereof.

22. The method of claim 21, wherein said pharmaceutical composition is administered intraoccularly.

23. The method of claim 22, wherein said pharmaceutical composition is administered at least once daily.

24. The method of claim 23, wherein said pharmaceutical composition is administered up to three times daily.

25. An ophthalmic formulation, comprising a therapeutically effective amount of leukotriene antagonist, more particularly unsaturated hydroxyalkylquinoline acids, and pharmaceutical salts thereof, an effective amount of a buffer to maintain the formulation to a pH value of 5.5 to 7.5, preferably 6.0 to 7.1, and an effective amount of a preservative.

26. The formulation of claim 25, which is in the form of a solution, gel or ointment, wherein the leukotriene antagonist is Montelukast sodium, the formulation providing 0.01 to 10 mg, more preferably 0.1 to 5 mg of Montelukast per unit dose.